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13. *Abstract (Maximum 200 Words)* *(abstract should contain no proprietary or confidential information)*

Aromatase (CYP-19) is responsible for estrogen biosynthesis within breast tumor tissue. Aromatase and cyclooxygenase-2 (COX-2) are both overexpressed in human breast cancer, and increased levels of prostaglandin (PG) activates the CYP19 promotor and increases gene expression. We hypothesize that celecoxib, a selective COX-2 inhibitor, will decrease PG, decrease the expression of CYP19, and reduce estrogen biosynthesis within tumor tissue. To test this hypothesis, in DOD grant # DAMD17-01-1-0589, tumor tissue will be collected from breast cancer patients at the initial diagnosis, and again at the definitive surgery (lumpectomy or mastectomy) for breast cancer. In the 10-14 day interval before the definitive surgery, patients will receive celecoxib and tissue samples collected before and after treatment with celecoxib will be evaluated for gene expression of COX-2 and CYP19. If our hypothesis is correct, then expression of the CYP19 gene will decrease in response to celecoxib. This study will provide preliminary data to a) support a mechanism whereby COX-2 inhibitors decrease estrogen production within breast tumors by decreasing CYP19 expression; and b) provide the rationale for initiating larger chemoprevention and therapeutic trials of COX-2 inhibitors in high risk and breast cancer patients.

14. SUBJECT TERMS
None provided

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Award Number: DAMD17-01-1-0589

TITLE: The effect of Cox-2 inhibitors on the aromatase gene (CYP19) expression in human breast cancer

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Columbus, Ohio 43210-1239

REPORT DATE: June 2004

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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INTRODUCTION

This study will test the hypothesis that celecoxib, a selective Cox-2 inhibitor, will decrease PG, decrease the expression of CYP19, and reduce estrogen biosynthesis within tumor tissue. The primary objective of the study is to evaluate Aromatase (CYP19) and estrogen receptor (ER) gene expression by reverse-transcriptase polymerase chain reaction (RT-PCR) in response to a selective cyclooxgenase-2 (COX-2) inhibitor, celecoxib, in paired tumor tissue collected at the time of the initial diagnosis and at the time of definitive surgery for localized, non-metastatic breast cancer patients. The secondary objective is to evaluate the effect of celecoxib on the following biomarkers: estrogen receptor, progesterone receptor, Her-2/neu, Ki-67, COX-1, COX-2, CYP19, CD31, and PGE2, and Aromatase activity in paired tissue specimens by standard immunohistochemical methods. Targeted accrual is 34 patients. The first patient was enrolled on August 22, 2003. To date, five patients have been enrolled on the study.

BODY

All five patients have had definitive breast surgery; however, with only 5 patients enrolled, work on the correlative studies has not yet been initiated. The first interim analysis of the samples will be performed after 10 patients have definitive breast surgery.

It is acknowledged that accrual to the study has been slow. Two main issues have been identified as affecting accrual numbers. Firstly, the research staff reports that many patients are uncomfortable with reading the consent form. These individuals are undergoing an original diagnostic biopsy and have not yet been diagnosed with breast cancer. However, prior to undergoing the biopsy procedure, they are asked to review a lengthy consent form that discusses the treatment and tests they will undergo on this breast cancer study. We addressed our concerns with the OSU IRB, and were encouraged to implement an additional screening consent form that addresses only obtaining extra tissue samples during the patient's biopsy procedure. If the biopsy indicates breast cancer, the patient will then be asked to review the treatment consent form. Dr. Shapiro was notified of the IRB's approval of the new screening consent form on June 21, 2004. The use of the screening consent form will be implemented effective June 21, 2004.

Secondly, OSU pharmacy staff recently conducted a literature review regarding sulfa allergies and the study drug, Celebrex. This review indicated that the restrictions outlined in the protocol related to the use of Celebrex in patients who report a sulfa allergy may be too restrictive, and may unnecessarily exclude patients from the study. Therefore, the protocol will be revised to reflect the current safety data in regard to Celebrex and sulfa allergies, and thereby exclude fewer patients from having the option of participating in the study.

The principal investigator remains committed to the scientific merit of this research study. He is confident that the study objectives will be met.

KEY RESEARCH ACCOMPLISHMENTS: None to Report at this time.

REPORTABLE OUTCOMES: None to Report at this time.

CONCLUSIONS: None to Report at this time.

REFERENCES: None to Report at this time.

APPENDICES: New screening consent form.

IRB Protocol No. 2001C0266
OSU Protocol No. OSU 0125

THE OHIO STATE UNIVERSITY

CONSENT TO INVESTIGATIONAL TREATMENT OR PROCEDURE

I, _____, hereby authorize or direct Dr. Charles Shapiro, or his associates or assistants of his choosing, to obtain tissue samples at the time of a breast biopsy upon _____.
(myself or name of subject)

The experimental (research) portion of the treatment or procedure is:

I have a breast mass or a spot or area of concern on my mammogram and my doctors have recommended taking a breast biopsy to see whether or not this area has breast cancer in it. My surgeon or the radiologist will perform a "core biopsy". He or she will numb my breast with medication and a very small cylinder of my breast tissue will be taken through a needle. The biopsy tissue is looked at under a microscope by a special doctor called a pathologist who determines whether there is breast cancer in the tissue. This biopsy is sometimes called a "diagnostic" breast biopsy. It is used to diagnose whether or not my breast tissue contains cancer cells.

I am being asked to allow my doctor to take 2-4 extra samples of tissue from my breast during my core biopsy procedure. I am being asked to allow this because if my biopsy results show that I have cancer cells in my breast tissue, and I may require treatment and I might be eligible to participate in a clinical trial called OSU 0125. This clinical trial looks at the drug celecoxib (Celebrex) to see whether or not it will have any affect on breast cancer tissue when taken prior to breast surgery. These extra core biopsies will be used for research purposes should I decide to enroll on OSU 0125. If I choose not to participate in the study, the extra core biopsies samples would be destroyed. If my biopsy results show that I do not have cancer in my breast tissue, I would not be able to participate in OSU 0125 and the extra core biopsy samples would be destroyed.

If the spot or area of concern on my mammogram cannot be felt by hand, the core biopsy will be obtained using ultrasound guidance. The ultrasound procedure is considered the standard of care when the area of concern in the breast cannot be felt by hand. A clear gel is placed on the breast and a hand held instrument called a "sound head" is placed on the skin of the breast. The ultrasound procedure uses sound waves to help localize the area of concern and helps my doctor determine the exact area he or she wants to biopsy.

The normal number of core biopsies taken when evaluating breast tissue for cancer is between 2 and 4. I am being asked to let my doctor take up to 6-8 core samples (between 2 to 4 extra samples) during my biopsy procedure. Two of the core biopsy specimens will be evaluated by the pathologist to determine whether there are breast cancer cells in my tissue. The remaining 4 cores will be used for research purposes should I decide to participate in the clinical trial OSU 0125. If 6 core biopsy specimens cannot be obtained within 8 biopsy attempts, the doctor will stop the biopsy procedure. If the doctor is unable to obtain additional core biopsy specimens from my breast tissue, I will not be eligible to participate in OSU 0125.

If the pathologist determines that more tissue is needed following the evaluation of the first 2 cores, he/she will use the extra core biopsy specimens that were taken for research purposes to evaluate them under the microscope. A special group, called The OSU Tissue Procurement Service, will maintain my core biopsies until the pathologist makes an accurate diagnosis. The purpose of the Tissue Procurement Service is to provide an organized structure for accessing human tissue and to provide quality specimens and pathology data while maintaining patient confidentiality. The Tissue Procurement Services collects and stores malignant, benign, diseased, and normal tissues.

My participation in OSU 0125 would be completely voluntary. If I choose to participate in OSU 0125, tissue samples taken from my breast cancer tissue must be obtained before I start the study treatment. If I have extra core biopsies taken during my diagnostic biopsy procedure, those tissue samples could be used if I decide to participate in OSU 0125. If I decide not to participate in the OSU 0125 study, none of the extra tissue biopsies I have taken will be used for research purposes. They will be destroyed.

This is done as part of an investigation entitled:

THE EFFECT OF CELECOXIB (CELEBREX®) ON THE AROMATASE GENE (CYP19) EXPRESSION IN HUMAN BREAST CANCER.

1. **Purpose of the procedure or treatment:**

   The purpose of this procedure is to obtain up to 4 additional core biopsies of my breast tissue to be used for research purposes should I decide to enroll on OSU 0125 in the future.

2. **Possible appropriate alternative procedure or treatment (not to participate in the study is always an option):**

   I am not required to allow my doctor to take additional core biopsies of my breast tissue. My care will not be affected in any way if I choose not to have additional core biopsies taken. I may call the doctor that is running this research study, Dr. Charles Shapiro (614-293-7530), at any time with any questions or concerns that I may have about having these extra core biopsies done. In addition, I may call the Ohio State University Institutional Review Board (614-292-5958) with any questions about my rights related to signing this consent form and having extra

core biopsies taken of my breast tissue.

3. Discomforts and risks reasonably to be expected:

This biopsy procedure is the standard way in which breast tissue is evaluated to see if the tissue contains breast cancer. I will have a breast core biopsy done even if I decide not to allow the extra core biopsies to be taken during the procedure. I will be monitored closely during the biopsy procedure. If symptoms develop, my doctor will give me the care that I need. A core needle breast biopsy may cause some discomfort, bruising, and involve a small risk of bleeding at the site of the biopsies. It is rare, but the skin at the biopsy sites may become infected. I should tell my doctor about any symptoms that develop related to the site of the breast biopsies. If I do allow the extra biopsies to be taken, it is possible that I may have some additional bruising, bleeding, and a small risk for infection at the site of the biopsies.

Every effort will be made to protect my privacy and maintain my confidentiality related to the breast core biopsies taken for research purposes. If my biopsy results indicate that my breast tissue contains breast cancer, and I decide to participate in clinical trial OSU 0125, my tissue samples taken for research purposes will be coded with a unique identification number. All results of the research studies performed on my breast tissue samples will be stored in a computer, and only Dr. Shapiro, who is running the study, the research nurse who is coordinating the study, the data managers who enter the results into the computer, the study sponsors, and required federal regulatory agencies will have access to this computer data. When the results of the study are compiled, my name will not appear and will not be included in the computerized database and data reports, manuscripts, or publications. Instead, the unique identification number will used. All results of clinical study OSU 0125 will be stored for a minimum of 3 years in a secured location.

4. Possible benefits for subjects/society:

I may receive no personal benefit from participating in the extra core biopsies. If my results show that I do not have cancer cells in my breast, or I choose not to participate in OSU 0125, the extra biopsies will not be used. They will be destroyed. In that case, I will have undergone an invasive procedure for tissue samples that will not be used. If I do participate in OSU 0125, the information obtained from the study may benefit the future of cancer; breast cancer in particular. However, there is no guarantee that I will receive direct benefit from the study treatment I would receive on OSU 0125.

5. Anticipated duration of subject's participation (including number of visits):

My participation in the extra core biopsies should involve no additional clinic visits beyond the one I will have for my diagnostic breast biopsy. My clinic visit may run approximately 30 minutes longer if I participate in the extra core biopsies.

COSTS AND INSURANCE

All of the costs related to my breast evaluation such as doctor and/or clinic visits, screening tests, blood work, radiographic scans, and pathology tests that are done to rule out or to confirm the diagnosis of breast cancer, will be my responsibility and will be submitted to my insurance company. I will not be responsible for any charges related to the extra 2-4 core biopsy specimens taken for research purposes. I will not be paid for having the extra core biopsies taken.

TERMINATION OF PARTICIPATION

My participation in having the extra core biopsies is completely voluntarily. If for any reason, at any time, I change my mind about participating in the extra biopsies, I can tell my doctor and I will not have the extra biopsies taken. My doctor can, for medical reasons, or if he or she feels that continuing to participate in the biopsies would not be in my best interest, end my participation at any time. It is possible that new information will arise during the OSU 0125 clinical trial that could influence whether I wish to participate in the extra biopsies. Dr. Shapiro will tell me and/or my doctor about any new information as soon as it is available, and he or my doctor will discuss the information with me.

I hereby acknowledge that _____ has provided information about the procedure described above, about my rights as a subject, and he/she answered all questions to my satisfaction. I understand that I may contact Dr. Stephen Povoski at Phone No. 614/293-8700 should I have additional questions. He/She has explained the risks described above and I understand them; he/she has also offered to explain all possible risks or complications.

I understand that, where appropriate, the U.S. Food and Drug Administration may inspect records pertaining to this study. I understand further that records obtained during my participation in this study that may contain my name or other personal identifiers may be made available to the sponsor of this study. Beyond this, I understand that my participation will remain confidential.

I understand that I am free to withdraw my consent and participation in this project at any time after notifying the project director without prejudicing future care. No guarantee has been given to me concerning this treatment or procedure.

I understand in signing this form that, beyond giving consent, I am not waiving any legal rights that I might otherwise have, and I am not releasing the investigator, the sponsor, the institution, or its agents from any legal liability for damages that they might otherwise have.

Questions about this should be directed to the Office of Responsible Research Practices at (614) 688-4792.

I have read and fully understand the consent form. I sign it freely and voluntarily. A copy has been given to me.

Date _____ **Time** _____ **AM / PM** **Signed** _____
(Subject)

Witness(es) _____ _____
If required ***(Person Authorized to Consent for Subject if Required)***

_____

I certify that I have personally completed all blanks in this form and explained them to the subject or his/her representative before requesting the subject or his/her representative to sign it.

Date _____ **Signed** _____
(Signature of Project Director or his/her Authorized Representative)